

**EVALUATION OF PATIENT RECRUITMENT STRATEGIES FOR
NIH INTRAMURAL EARLY PHASE CLINICAL TRIALS**

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SECTION 1

1.2 Programs to be Evaluated

The Patient Recruitment and Public Liaison Office (PRPL), Clinical Center and the **Clinical Studies Support Center (CSSC), CCR, NCI** are two offices established for the purpose of assisting intramural investigators recruit patients to their studies. Because both programs have been in existence for the same period of time and have available data on the results of specific strategies employed to recruit patients to NIH intramural studies, the patient recruitment strategies of these programs are being evaluated.

These two programs have been in operation for approximately 7 years and operate on a request for service basis. They conduct recruitment campaigns for protocols within the NIH intramural program. Each program has a budget of approximately \$1.5 million including staff salaries. The **PRPL** provides services to investigators across institutes while the **CSSC** recruits patients to NCI studies.

PRPL and **CSSC** services include:

- ◆ Recruitment planning and implementation
- ◆ Toll free telephone information and referral service (call center)
 - Information and referral for active Clinical Center studies.
 - Service in English and Spanish
- ◆ Telephone Prescreening
 - A first step in determining caller eligibility.
- ◆ Database Searches (from PRPL application)
 - Contact lists of potential patients, or healthy volunteers who have expressed interest in participating in your?? specific? areas? of research. Lists of physicians who have referred patients with specific diagnoses.

The PRPL provides:

- ◆ Clinical Research (Healthy) Volunteer Program
 - Assists in recruiting, registering, and compensating volunteers for study participation.

Each office develops and conducts patient recruitment activities based on the requests of the individual investigator, a review of the protocol, and the intended target audience(s). Recruitment for a particular study may consist of the implementation of one or more strategies including advertising (print, radio, internet), outreach to patient support groups, dissemination of protocol information to physicians and community organizations, presentations, physician seminars, collaborative agreements between NIH and healthcare organizations for patient referrals. These strategies may be implemented simultaneously or sequentially, based on the request of the investigator, and the available budget. The PRPL also conducts an annual advertising campaign (print, radio and internet) for selected diseases.

The programs operate separate call centers where staff respond to protocol inquiries and refer prospective patients to studies. During FY03, the CSSC handled approximately 1000 phone calls and 70 emails per month, the PRPL dealt with 2300 calls, 1530 emails and 10 faxes per month.

Each program collects its own data about patient recruitment strategies and outcomes for different protocols or clusters of protocols.

1.2.1 Project Goal

This project will constitute the first attempt to gather and combine retrospective data from both programs, and possibly other Institutes in the future, in order to

- evaluate the effectiveness of recruitment strategies across protocols and institutes,
- design a prospective study based on initial findings,
- develop methods to gather recruitment data in a standardized manner.

1.2.2 Project Rationale

This project is proposed because clinical trials are a crucial component in the research, development, and evaluation of disease treatment strategies. However, clinicians and researchers have historically experienced problems in recruiting adequate numbers of participants to clinical trials.

In fact, patient recruitment is one of the most significant bottlenecks in treatment development. Many patients who would be eligible to participate never have the opportunity to do so, and most potential patients do not know that a clinical trial might be a treatment option for them. In addition, many physicians aren't aware of the clinical trials available to their patients, thereby making it less likely that their patients will participate.

Slow or insufficient patient enrollment in clinical trials contributes significantly to the slow rate of completion and occasional failure of some trials (Spilker & Cramer, 1992). In 2000, for example, an estimated 78 percent of all clinical studies failed to enroll the required number of patients on time (Getz, 2000). The costs of failed or delayed trials include not only wasted resources that were allocated to them, but also the costs of participants' time and discouragement of primary care professionals from cooperating with further research.

Recruitment and retention of patients for clinical research at the CC has become more difficult (Gallin and Varmus, 1998). Recruitment to CC trials faces additional challenges because unlike major medical centers that rely on their own patients, affiliated physician networks or faculty, the CC must recruit patients directly from external sources. In the past, most patients were referred by community physicians. However, the advent of managed care and the increased number of clinical trials being conducted by major

medical centers and pharmaceutical companies result in the need to initiate other strategies to recruit patients.

In 1996, the CC's Medical Executive Committee (formerly, the Medical Board) identified patient recruitment as a major barrier to the completion of clinical trials, particularly early phase studies (Phase I and II) which comprise 90% of the intramural research portfolio. As a result, centralized recruitment offices were established by the CC, NCI and NIMH in an effort to improve study enrollment, and respond to the congressional mandate to increase participation of women and minorities in clinical trials.

In addition to the efforts of the recruitment offices, patient recruitment continues to be carried out in a decentralized fashion by research nurses and principal investigators across institutes. Each entity operates in relative isolation, and little is known to date about methods used to capture data regarding strategies, cost, and return on investment of patient recruitment efforts.

This fact plus the paucity of information in the literature makes it difficult to predict outcomes or determine the most successful or best recruitment practices for different studies conducted across the NIH intramural program.

Though a difficult undertaking, this project marks the first known effort to collect, compare and contrast recruitment strategies and results across protocols. The project will capture and compare recruitment data, initially from two offices and subsequently from other investigators across the intramural program.

1.2.3 Level of Clinical Center (Intramural) Clinical Trial Activity

Fifteen institutes have active clinical protocols at the Clinical Center. Approximately 1000 protocols are being conducted across institutes. Eighty-nine percent of these protocols are actively recruiting subjects at any given point in time. The intramural research (FY2002) portfolio consists of clinical trials (44%), natural history (49%), screening (4%), and training (3%) protocols. Of the active clinical trials, 35% are Phase I, 55% are Phase II, 7% are Phase III and 3% are Phase IV.

The patient recruitment evaluation will be led by Tracy Thompson, NCI and Dorothy Cirelli, Clinical Center. The project is being undertaken with the approval of the Clinical Center Director, the NCI Center for Cancer Research Director, and the Clinical Center's Medical Executive Committee. This initiative is envisioned as a multi-year project with the initial phase (approximately 6 months) focused on an analysis of PRPL and CSSC retrospective data.

1.3 Program Goals

Goals of the PRPL and CSSC are to:

1. Increase patient enrollment by developing effective advertising and outreach strategies for protocols and improving the patient referral process
2. Comply with Federal guidelines to increase participation of women and minorities in clinical trials.

SECTION 2

2.1 Type of Evaluation

This is a multi-phase, multi year project beginning with a phase one feasibility study of existing patient recruitment methods and strategies employed by the Patient Recruitment and Public Liaison Office (PRPL), CC and the Clinical Studies Support Center (CSSC), NCI. This proposal requests funding support for phase one activities.

Phase one of the project will collect base-line data for an established time period prior to the initiation of recruitment strategies, during implementation, and the same period of time following implementation of recruitment strategies to identify those that resulted in the largest number of contacts, referrals and enrollments to studies. Phase one includes 5 activities:

- Development of the research design (statistical analysis).
- The identification of key variables by which to categorize and compare PRPL and CSSC recruitment data, e.g. common vs. rare disease.
- Determining the quantity of data needed in each of the data categories to perform a statistical analysis of recruitment outcomes.
- Conducting the data analysis.
- Reporting the results and recommendations.

Phases 2 will be conducted based on the results of phase one.

Phase 2: The project leaders will design and conduct phase two, a prospective study to “test” the hypotheses developed as a result of the initial phase one evaluation. For example, phase two may involve the testing of different types or a combination of advertising or outreach strategies proven effective in phase one for certain diseases, clinical trial phase or patient demographic.

To the degree that best strategies cannot be identified, the project leaders will develop a plan and recommendations to collect needed data to develop and test patient recruitment strategies thought to be effective.

2.2 Purpose of Evaluation

To date, no systematic review and analysis of the success of various NIH patient recruitment strategies for particular categories of protocols, populations (including women and minorities), diseases, audiences, etc. has been conducted. The purpose of the phase one feasibility study is to:

- Gather and evaluate recruitment data from the PRPL and CSSC for specific disease populations to identify best recruitment strategies for protocols.

- Gather and evaluate recruitment data from the PRPL and CSSC for specific population parameters (ethnicity, gender, specific age ranges) to identify best recruitment strategies for protocols.
- Establish guidelines for investigators who independently plan patient recruitment efforts for their protocols.

The completion of the phase one evaluation will result in the initiation of the subsequent phases of this project in order to:

- Test those strategies identified in phase one as “best” or “successful”.
- Standardize methods and systems by which institute staff collect and report patient recruitment data.
- Link various systems throughout the intramural program containing recruitment strategies data with CC accrual information (CRIS) enabling investigators to gain information about the results of their recruitment efforts as well as a broad based analysis and evaluation of the success of recruitment strategies across the intramural program.

The long term goal of the project is to develop an evidence-based systemized approach, using an analysis of historical and prospective data that will assist investigators in selecting patient recruitment strategies that will result in optimal patient enrollment to their particular study.

2.3 Use of Results

The results of this initial evaluation and the subsequent phases of this project will provide:

- Evidence based guidance for NIH investigators to direct future recruitment efforts.
- Development of a systematic, trans-NIH approach to data collection and evaluation of recruitment efforts.
- Application of the rigors of the scientific method to a process that, even with the best market research and application of marketing and public relations principles, is costly and time-consuming when conducted in isolation on a trial and error basis.
- Publications that will assist any investigator with patient recruitment efforts.

It is reasonable to expect that all ICs performing clinical trials within the NIH Clinical Center will benefit from this study. Principal Investigators who consult with the PRPL and CSSC, as well as those who do not, will be able to refer to the study results in determining how best to recruit patients for their protocol in the most efficient and cost effective way.

2.4 Review of the Literature

The review, which has already been completed with NCI funds, encompassed searching computerized databases (MEDLINE, PUBMED), Internet sites (www.nih.gov; cancer.gov; www.asco.org) and reference lists from retrieved articles. The search keywords included *phase I clinical trials*, *phase II clinical trials*, *clinical trials recruitment*, and *clinical trials and media coverage*. In addition, a number of unpublished NCI reports, including focus group reports and conference reports, were reviewed.

The collected articles pertained primarily to barriers and obstacles to patient recruitment in clinical trials. A large number of articles were devoted to issues related to minority patient accrual. Content pertaining to successful patient recruitment strategies, however, was mostly anecdotal.

Patient accrual is affected by factors related both to people (i.e., patients, principal investigators, research nurses, referring physicians) and to activities (e.g., protocol design, recruiting outreach, patient screening, informed consent, medical procedures). Difficulties in clinical trials patient recruitment in general, and early phase cancer trials recruitment in particular, are a significant barrier to treatment development. The literature about this problem and what can be done to improve recruiting overall is characterized by significant gaps and limitations. Although all of the studies described in this review help to illuminate the issues, most of them relied upon research techniques that make generalizations to a larger population tenuous.

Cancer patients participating in phase I and II clinical trials are usually referred to clinical research by their physicians, although an unknown percentage of participating patients are self-referred. Anecdotal and unpublished reports suggest that interpersonal relationships and outreach among medical professionals are also important to recruiting, but the topic is not addressed in the literature.

A number of additional strategies may be employed by investigators to recruit participants, although it is unknown how those differ among different phases of cancer or other clinical trials. Among them are mass mailings to patients and physician practices, study notices and bulletins, radio, television, internet and newspaper ads, public service announcements, fliers, and websites. In some cases, those recruitment strategies may be supplemented with public relations campaigns to help increase awareness of the project in the communities studied. Such outreach strategies might include media-related activities, such as placement of news stories, or community presentations as forums for key opinion leaders in the communities to endorse the study among their constituents (Lewis et al., 1998; Pentz, et al., 2002; Schoen, 1999). The strategy or combination of recruitment strategies employed is influenced by available funds, the nature of the targeted patient population, the trial's timeframe, and the number of required subjects (Spilker & Cramer, 1992).

Little systematic research exists on the effectiveness of various recruitment methods to clinical trials in general, and to early phase trials in particular. In most instances when such information is provided, it is anecdotal rather than systematic, and/or pertains to phase III clinical trials. Also, although such analysis is not available for the early phase trials, a review of general randomized trials reports (Gross et al., 2002) suggested that investigators rarely documented how many people were identified as eligible for

enrollment, and the number of potential participants that needed to be screened to identify one enrollee.

Furthermore, a study of methods utilized in patient recruitment to randomized controlled trials (Foy et al., 2003) found that the recruitment methods used by the investigators were not evidence-based, and that organizational characteristics, such as previous research experience or patient eligibility criteria, could be more influential in trial recruitment than the use of specific interventions. No similar analysis has been conducted for the phase I or II clinical trials, and these gaps in the literature clearly suggest that further research is necessary to discern the effectiveness of various recruitment methods for the early phase clinical trials.

2.5 Timeliness of the Evaluation

Now more than ever, NIH intramural investigators are sensitized to the need to improve recruitment to studies conducted at the Clinical Center. Despite the successes of centralized recruitment offices and an increase in patient recruitment activities, many studies are slow to accrue patients. The planned opening of the NIH Clinical Research Center emphasizes the need to approach the problem of under-recruitment in a systematic evidence-based way.

As the government's premier research facility, the NIH Clinical Center provides a superb, unique environment for clinical research, particularly early phase clinical trials. In order to advance the NIH mission, the new Clinical Research Center must be used to its full capacity, therefore it is imperative to increase awareness of the intramural program and the studies available to the public.

Many NIH investigators are frustrated because they are uncertain as how to spend the limited budgets that they have to recruit patients. Others continue to implement outmoded or ineffective strategies. Some are confused because strategies that worked well for a colleague's protocol produced few patients for their study. On the other hand, those strategies that have proven effective are not widely known or communicated.

Dr. Zerhouni's roadmap encourages scientists to make changes in the way they approach the scientific enterprise by developing new research partnerships with organized patient communities, community-based health care providers, and academic researchers. He stresses the need to build better integrated networks with academic medical centers and community-based physicians who care for sufficiently large groups of patients who may be willing and available to participate in medical research.

In this context a project such as the one described here is timely and essential for NIH to fulfill its mission.

SECTION 3

3.1 Study Questions

The key question to be addressed in Phase One:

What recruitment strategies result in the greatest number of contacts, referrals and enrollments for various categories of protocols?

To answer this key question, the following must additionally be answered.

- What data (contacts, referrals, enrollments and recruitment strategies per study) are available from the PRPL and CSSC?
- How do we define success for recruitment efforts?
- How can data be categorized for analysis, e.g. by disease, by study characteristics, by patient characteristics?

3.2 Target Population

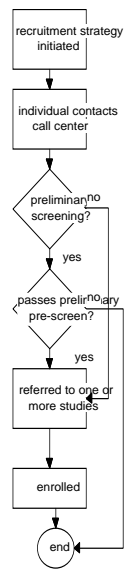
Phase one of this project will collect and compare the patient recruitment strategies initiated by the PRPL and CSSC for different categories of early phase clinical trials (phase 1 and phase 2) conducted by the Institutes that comprise the intramural program. Many institutes and populations, depending on the amount of available data, will be represented in the analysis. The evaluation will consist of a retrospective analysis of patient recruitment strategies used to recruit the target patient populations identified in the various protocols.

3.3 Key Variables

- 1) Number of calls to call center per trial;
- 2) Number of subjects accrued per trial;
- 3) Promotion method used to recruit patients;
- 4) Source patient used to get information about trial (e.g., internet, newspaper);
- 5) Trial information (e.g., phase, disease, invasiveness of treatment), for example, inclusion/exclusion criteria for patients being excluded;
- 7) Demographic information about patients who called/were accrued (e.g., age, gender).

This first analysis is exploratory in nature and intended to identify key variables, beginning with recruitment strategies that affect accrual to clinical trials. As the analysis proceeds, other variables will be identified and incorporated into phase two of the project.

3.4 Conceptual Framework



SECTION 4

4.1 Data Sources

Phase One data will be collected from PRPL and CSSC archival data. These data currently consist of information from each program's respective call center and are currently stored in each program's own database application.

4.2. Data Collection Strategies

Strategies used by each protocol to recruit subjects will be extracted and coded into meaningful categories. Protocols will be stratified by patient characteristics (e.g., age, gender), diseases characteristics (e.g., rare vs. common), and protocol characteristics (e.g., invasiveness, phase) using pre-defined coding schemes as agreed upon by pertinent study personnel in a manner that allows for a significant number of protocols to be included in each category

4.3. New Data Collection Instruments

Not applicable for Phase One

4.4. Clearance requirements

Not applicable

4.5 Data Integrity

Given that the original data for Phase One are archival, data integrity will be best assured by working closely with CSSC and PRPL staff and our advisory committee when extracting the data. The advisory committee will also assist in defining “success” for recruitment strategies.

Regarding accuracy, existing data will be re-classified into meaningful categories as delineated by a pre-defined coding scheme (e.g., classifying a protocol as recruiting for a common vs. a rare disease). To ensure reliability, whenever possible, data will be cross-verified with multiple raters trained by project staff.

Regarding completeness of the data, its archival nature makes it difficult to fill in gaps, though extrapolation may be used as necessary if supporting data are available. Though we will attempt to minimize missing data, incomplete data and/or gaps that need to be filled will be very instructive and will inform the type of data needed for future data collection efforts of this project.

4.6. Ethical Considerations

Not applicable. There are no personal identifiers that would raise concerns about confidentiality. There is no additional burden placed on the respondents given that these are archival data. Data shall be extracted in such a way that information will not be identified.

4.7 Data Preparation

Data will be entered into a spreadsheet using information from a codebook created by project staff. This codebook will delineate valid and missing values for each variable that will consist of both closed and open responses. Once entered, the data can be imported

into a statistical program such as SAS or SPSS where quality control checks such as examining the data for out of range values and/or missing values will be performed using descriptive statistical procedures.

4.8 Data Analysis

The first analyses will include univariate descriptive statistics of the available data, using both measures of central tendency and variability for continuous variables, and frequencies for categorical variables. From this, data can then be stratified by important categories (e.g., disease type) and then used in other descriptive procedures (e.g., means or cross-tabulation tables) against outcome variables such as number of subjects accrued or disease type. If the data are found to be adequate, other analyses will be performed to address issues such as best predictors of accrual and/or number of calls for a particular clinical trial.

SECTION 5

5.1 Products of the Evaluation

The results of the evaluation will be the identification of successful/best recruitment strategies, in terms of the number of contacts, referrals and enrollments, by type of protocol. This information will serve as baseline for the development of a prospective study and the development of methods to collect improved recruitment outcome metrics. Phase one will also identify protocol and other factors that enhance or inhibit recruitment efforts.

5.2 Dissemination of Results

The results of Phase One Analysis and recommendations will be summarized in a report and disseminated to the Director, Clinical Center, the Director, Center for Cancer Research, NCI and the Clinical Center's Medical Executive Committee (MEC). The MEC includes the Clinical Directors of every NIH IC. If appropriate, the recommendations/results will be published in a peer-reviewed journal, posted on an NIH website, and/or sent via e-mail to all NIH Principal Investigators. If posted on a website, announcements of the location may be advertised, if appropriate. It may also be presented at a national clinically-based professional society meeting.

SECTION 6

6.1 Project Implementation

The project will be managed by Tracy Thompson, CCR, NCI and Dorothy Cirelli, PRPL, CC. Rick Moser, an NCI statistician will provide guidance regarding study design and statistical analysis.

A Statement of Work will be developed and contract proposals solicited from the vendor community via the GSA schedule. The contractor(s) will be selected based on a review of prior work experience and performance.

6.2 Advisory Committee

Given the scope and complexity of this project, an advisory committee will be needed to direct and develop the inter-institute collaboration needed to successfully complete this project. Members will include 7-10 individuals selected through recommendations by Institute Clinical Directors and the Project Managers who have expertise in any of the following: qualitative and quantitative research, research methodology and design, statistics, database design, project management, communications, patient recruitment. The committee will provide recommendations to the Project Managers about the planning, execution and evaluation of contract activities and assist in the communication of those activities to the NIH intramural community. The advisory committee will meet quarterly to receive updates on the projects or as needed.

6.3. Estimated timeline for the Evaluation

Once the contract is awarded, completion of Phase One of this project will take an estimated eight months. The time may need to be extended due to procurement, data collection and categorization difficulties, and the scheduling of Advisory Committee meetings.

Timelines are as follows:

Task	Timeline
Development of research design	Month 1-2
Data collection and categorization	Month 3-5
Data Analysis	Month 6-7
Development and review of the final report	Month 8

SECTION 7

7.1 Estimated Costs

It is anticipated that, if funded, the contract will be awarded in August or September of 2004. Therefore, approximately \$16,000-\$20,000 will be spent in FY04 with the remainder of funds spent in FY05. However, all funds will be obligated in FY04.

Phase 1**A. Table 1. Direct Labor Costs**

Staff	Hours	Hourly Rate	Cost
Project Manager	312	60	\$18,720
Statistician	550	50	\$27,500
Statistical Support	1000	25	\$ 25,000
Coder (2)	100	20	\$ 4,000
Administrative Support	200	18	\$ 3,600
Writer	80	30	\$ 2,400
Salary Costs			\$81,220
Fringe benefits	25% of salary		\$20,305
a. Salary & Benefits			\$101,525

Table 2. Other Direct Costs

Computing			\$5,000
Travel			\$200
Copying			\$5,000
Supplies			\$3,500
b. SUB TOTAL			\$13,700
TOTAL DIRECT COSTS (a&b)			\$115,225

Table 3. Indirect Costs

Overhead	65% of direct costs		\$69,802
G&A	15.5% of direct costs		\$15,645

Fee	8% of direct costs		\$8,591
c. Total: INDIRECT COSTS			\$94,038
TOTAL COSTS:PHASE 1			\$209,263

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